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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,663	01/10/2002	Robert P. Kimberly		2937

7590 08/24/2004

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,663	KIMBERLY ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6-3-04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *1-3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-9* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response to the restriction requirement filed 6-3-04 has been entered into the record.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 4-9 of this application. It is noted in particular that the species of SLE in the provisional document does not support written description and enablement for the now claimed genus of autoimmune diseases. Further, the first line of the specification recites 60/260,823 which does not have an inventor in common with the instant application. It is noted that the oath recites the provisional document 60/260,832 which does have an inventor in common. Correction and clarification is required with respect to this issue.

Drawings

The drawings in this application have been approved by the Draftsperson.

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The use of the trademarks BlyS™ and Sepharose™ have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Information Disclosure Statement

No information disclosure statement has been filed in this application.

Election/Restrictions

Applicant's election of Group II, claims 4-9 in the response of 6-7-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-3 have been withdrawn from consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting systemic lupus erhthramatosus (SLE) by quantitation of BLyS™ it does not reasonably provide enablement for the genus of patient displaying symptoms of autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to methods of monitoring changes in a condition of a patient displaying symptoms of autoimmune disease by evaluation of the level of the levels of BLyS™ in sera or plasma from patients using an immunoassay. The teachings of the specification are limited to increases in BLyS™ in sera or plasma from SLE patients and the correlation with anti-dsDNA antibodies. The specification only enumerates SLE and Sjorgen's syndrome (SS) as self-antigen driven autoimmune diseases. It is noted that these diseases contain disparate clinical squeleae, pathology and etiology. While the art teaches that there are autoantibodies held in common with SLE and SS (Fundamental Immunology Second Edition, Paul ed, pages 837-840, Raven Press 1989), the specification does not describe a correlation of these autoantibodies with levels of BLySTM. correlative autoantibodies in common. In other words, the anti-dsDNA antibody that is correlative with SLE can not be correlative or predictive of levels of BLySTM with patients having SS because it is not observed in this disease. The specification fails to describe a correlation of levels of BLySTM with any of the autoantibodies held in common with SLE and SS and as such SS can not be predictably correlated with increases in BLyS™ and therefore can not be used to monitor disease. None of the autoantibodies known to be held in common between at least these two diseases have been correlated to levels of BLyS™ and these autoantibodies are not pathogenic. Pathogenic as opposed to generic autoantibodies participate in the disease process and levels of the pathogenic autoantibodies (i.e. anti-dsDNA antibodies) are not described by the specification in relation to specific levels of disease activity for SLE. The specification fails to teach that

the levels of anti-ds-DNA and levels of BLyS™ contribute to disease activity because the disease level of the specific patient was not assessed and all patients were classified as having SLE (see page 4, lines 10-25) but not assessed for actual disease activity per se. The ability to accurately gauge disease activity retrospectively is suspect to interpretation (see Cheema et al (Arthritis and Rheumatism, 44(6):1313-1319, June 2001) page 1319, column 1). Additionally, Zhang et al (Journal of Immunology, 166:6-10, January 2001) teach that increased BLyS™ was "not associated with the disease activity" (see abstract). There is no data presented in the specification relating to disease activity, autoantibody levels and BLyS™ levels. As such, it is not clear from the teachings of the specification if BLyS™ levels either increase or decrease with changes in disease activity (i.e. the condition of a patient). There is no data presented for SS and it remains unclear if these patients have increase or decreases in BLyS™ and how this relates to any marker of the specific autoimmune disease or disease activity. Additionally, the term self-antigen driven autoimmune diseases encompasses autoimmune disorders such as graft-versus-host disease where the immune response is self antigen driven. There is no described autoantibody or BLyS™ associated with this disease that corresponds to the described SLE autoantibodies. There are no common markers between any of these diseases and as such, the description for SLE can not be extended to the genus on the basis of similar "autoimmune disease". Each disease has different pathologies and the specification fails to establish the level of BLyS™ as a commonality in the detection, diagnosis, progression or regression of "self-antigen driven autoimmune disease" as is claimed. One skilled in the art would have to test to establish a correlation with disease activity in a representative number of self-antigen driven autoimmune diseases in order to obtain information regarding the disparate diseases in this category and any potential link to levels of BLyS™. The courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 153 USPQ 48). Applicants' have no written description for any of these other correlations to

disparate autoimmune diseases and their disease activity (i.e. as it relates to the instant monitoring the changes in condition of a patient displaying symptoms of autoimmune disease) which lack a common disease marker/pathology or etiology with the disclosed SLE and therefore are not enabled for such. Applicants' are not entitled for dominance of further patentable inventions by claims that are insufficiently supported by the specification (*In re Fisher*, 166 USPQ 18, CCPA (1970)). In applications directed to inventions in arts but where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species for the detection of SLE it is not clear, what other species will work to monitor/prognoses/diagnose or detect.

In view of the lack of written description of the correlation of the level of BLySTM with disease activity in SLE, the lack of teaching of levels of BLySTM in any other autoimmune disease and their relation to disease activity, one skilled in the art would be unable to practice the invention as claimed because the specification does not teach that the level of BLySTM either positively or negatively correlates with disease activity and the claims should be limited to the detection of SLE *per se*.

Claims 4-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 4 and every dependent claims (claims 5-9) the following phrases lack antecedent basis in the claim or in the independent claim. In claim 4 "the product". In claim 5, "the test". In claim 7, "the support".

Further, as to claim 4, step 1 is unclear because it is unclear if both samples are independently contacted with anti-BlyS™ antibodies. The current claims merely require a control sample to be contacted with anti-BlyS™ antibodies. This issue may be resolved by amending the claims to recite contacting a sample from a patient and a control sample containing a known amount of BlyS™ with anti-BlyS™ antibodies. Incubating the samples and the anti-BlyS™ antibodies for a time sufficient o allow said anti-BlyS™ antibodies to bind BlyS™ in the samples. The claim is further confusing because it is unclear what a "self-driven autoimmune response to anti-BlyS™ antibody is. The specification does not enumerate or describe what these conditions are. As such the metes and bounds of this phrase can not be determined. Further, it is unclear what is meant by a control sample containing a known amount of BLyS™ to anti-BlyS™ antibodies. Is a specific ratio claimed? The specification does not describe specific rations. As such the metes and bounds of this phrases can not be determined.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the

> applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made

absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (Journal of Immunology 166:6-10, January 2001).

The claims are drawn to monitoring the changes in condition of a patient displaying symptoms of autoimmune disease where the method comprises exposing samples of plasma or sera from the patient with anti-BLySTM antibody, incubating and evaluating the amount of antibody bound to BLySTM in the sample, determining the amount of BLySTM in the sample.

Zhang et al teach elevated serum B-Lymphocyte Stimulator Levels in Patients with Systemic Lupus Erythematosus (abstract). Zhang et al teach that the levels of BLyS^{TM} in serum samples from patients with autoimmune disease were assayed using an antigen capture enzyme-linked immunosorbent assay (ELISA) using a monoclonal antibody as a capture reagent and a biotinylated rabbit anti-human BLyS^{TM} of antibody as the detector antibody, immunoprecipitation and western blotting (see Materials and Methods; page 8, column 1, Figure 2). Zhang et al teach that the assay was standardized by use of recombinant soluble of BLyS^{TM}. (see page 7, column 1). Zhang et al teach that there was a correlation between both the levels of BLyS^{TM} and SLE and rheumatoid arthritis (see page 7, column 2, Figure 1). Zhang et al teach increased levels of BLyS^{TM} in patients with symptoms of autoimmune disease. As such, the teachings of Zhang et al anticipate the instantly claimed invention because they represent a single monitoring time point and there is no correlative step recited in the claims relating levels to disease activity.

Claims 4-9 are rejected under 35 U.S.C. 102(e) as anticipated by Bletzer et al (US 2003/0091565, published 15 May 2003, filed 17 August 2001 with full priority to US Provisional 60/226,700 filed 18 August 2000).

The claims are drawn to monitoring the changes in condition of a patient displaying symptoms of autoimmune disease where the method comprises exposing samples of plasma or sera from the patient with anti-BLySTM antibody, incubating and evaluating the amount of antibody bound to BLySTM in the sample, determining the amount of BLySTM in the sample.

Beltzer et al teach methods and compositions for diagnosing, prognosing and/or monitoring diseases or disorders associated with aberrant BlySTM expression. Beltzer et al teach that the methods using the BlySTM binding polypeptides can employ the polypeptides attached, coupled, linked or adhered to a matrix, resin or solid support known to the art and include SEPHAROSE™, microtiter dish such as that used in an enzyme-linked immunosorbent assay (ELISA), and nitrocellulose (see [0191]). Beltzer et al teach that systemic lupus erythematosus (SLE) can be diagnosed (see [0199]). Beltzer et al teach that a "BlyS binding polypeptide" is a molecule that can bind BlyS target protein ([0235]). This definition is seen as inclusive of anti-BLyS™ antibodies. Beltzer et al teach Western Blot analysis for detection of BLyS™ in samples (see [0513]). Beltzer et al teach ELISA's for the detection of BLyS™ using anti-BlyS polypeptides and immunoprecipitation assays for detection of BLyS™ ([0514-0515]). Beltzer et al teach assaying the expression of BLyS™ in a biological sample from an individual , comparing the level of BLyS™ with a standard level of BLyS™ ([0544-0547]). Beltzer et al teach that elevated levels of soluble BLyS™ have been observed in serum of patients with (SLE) and most SLE patients had more than 5 ng/ml of serum BLyS™ and in contrast the majority of normal controls had BLyS™ levels less than 5 ng/ml, the soluble BlyS™ in the serum was able to stimulate anti-IgM treated B cells *in vitro*. SLE patients with more than 15 ng/ml

serum BLyS™ were also found to have elevated levels of anti-ds DNA antibodies. Beltzer et al teach that the results of the study suggested that an elevated level of BLyS™ precedes the formal fulfillment of the ACR criteria. ([0552-0554]). Further, Beltzer et al teach that the assay can be used to detect/diagnose/prognose Rheumatoid Arthritis [0555]. In order to quantitatively determine the absolute level of BLyS™ in a sample, the skilled artisan would immediately envision that the control sample as disclosed in the assay methods of Beltzer et al must necessarily have been "a sample containing a known amount of BlyS[™]" as recited in the claims. As such, the disclosure of Beltzer et al inherently anticipates the instantly claimed methods. As such, the teachings of Beltzer et al anticipate the instantly claimed invention because they represent a single monitoring time point and there is no correlative step recited in the claims relating levels to disease activity.

It is noted that the above identified passages are *ipsis verbis* in the provisional document.

Claims 4-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheema et al (Arthritis and Rheumatism, 44(6):1313-1319, June 2001).

The claims are drawn to monitoring the changes in condition of a patient displaying symptoms of autoimmune disease where the method comprises exposing samples of plasma or sera from the patient with anti-BLySTM antibody, incubating and evaluating the amount of antibody bound to BLySTM in the sample, determining the amount of BLySTM in the sample.

Cheema et al teach elevated serum B-Lymphocyte Stimulator Levels in Patients with Systemic Immune-based Rheumatic Diseases (abstract). Cheema et al teach that the levels of BLyS™ in serum and synovial samples from patients with autoimmune disease were assayed using an antigen capture enzyme-linked immunosorbent assay (ELISA) using a monoclonal antibody as a capture reagent and a biotinylated rabbit anti-human BLyS™ of

antibody as the detector antibody. Cheema et al teach that the assay was standardized by use of recombinant soluble of BLyS™. (see page 1314, column 2). Cheema et al teach that there was a correlation between both the levels of BLyS™ and anti-double stranded DNA or rheumatoid factor titers (see page 1317, column 1, Figure 3). Cheema et al teach increased levels of BLyS™ in patients with symptoms of autoimmune disease. The teachings of Cheema et al anticipate the instantly claimed invention because they represent a single monitoring time point and there is no correlative step recited in the claims relating levels to disease activity.

Claims 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheema et al (Arthritis and Rheumatism, 44(6):1313-1319, June 2001) in view of Bletzer et al (US 2003/0091565, published 15 May 2003, filed 17 August 2001 with full priority to US Provisional 60/226,700 filed 18 August 2000).

Cheema et al is set forth *supra*. Cheema et al differs by not teaching assay of BLyS™ by immunoprecipitation or western blot.

Beltzer et al teach detection of BLyS™ immunoprecipitation and western blotting. Beltzer et al teach that a "BlyS binding polypeptide" is a molecule that can bind BlyS target protein ([0235]). This definition is seen as inclusive of anti-BLyS™ antibodies. Beltzer et al teach that the methods using the BlyS binding polypeptides can employ the polypeptides attached, coupled, linked or adhered to a matrix, resin or solid support known to the art and include SEPHAROSE™, microtiter dish such as that used in an enzyme-linked immunosorbent assay (ELISA), and nitrocellulose (see [0191]). Beltzer et al teach Western Blot analysis for detection of BLyS™ in samples (see [0513]). Beltzer et al teach ELISA's for the detection of BLyS™ using anti-BlyS polypeptides and immunoprecipitation assays for detection of BLyS™ ([0514-0515]).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to utilize any of the many different assay formats of

Beltzer et al including western blotting and SEPHAROSE™ immunoprecipitation to quantitate the level of BLyS™ in biological samples from autoimmune disease patients because Cheema et al teach that there was a correlation between both the levels of of BLyS™ and anti-double stranded DNA or rheumatoid factor titers (see page 1317, column 1, Figure 3) in systemic immune-based rheumatic diseases. The assays of Beltzer are obvious variants of the ELISA of Cheema et al. It would have taken no more than routine experimentation to substitute the serum in any of the contemplated assays of Beltzer et al in order to quantitate BLyS™ in a patient sample.

Status of the Claims

Claims 4-9 stand rejected and claims 1-3 are withdrawn from consideration as drawn to a non-elected invention.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-F 6:30 am - 3:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645